GMP/GDP Consultative Committee
Note of Meeting
30th October 2015, Room G-1, 151 Buckingham Palace Road, London.

Representatives from the following organisations were present at the GMP-GDP Consultative Committee meeting held at BPR on the 30th October 2015:

MHRA (Inspection, Enforcement & Standards Division)
Scottish Lifesciences Association (SLA)
Proprietary Association of Great Britain (PAGB)
Bio-Industry Association (BIA)
British Generic Manufacturer's Association (BGMA)
Association of Pharmaceutical Specials Manufacturers (APSM)
British Association of Pharmaceutical Wholesalers (BAPW)
Joint Professional Bodies QP Assessor Panel (JPB-QP)
Pharmaceutical Quality Group (PQG)
Association of the British Pharmaceutical Industry (ABPI)
Research Quality Association (RQA)
Veterinary Medicines Directorate (VMD)
Ethical Medicines Industry Group (EMIG)
The Cogent Group
NHS Technical Services
NHS Pharmaceutical QA Committee
National Office of Animal Health (NOAH)
National Assembly for Wales

1. Introduction

MHRA welcomed current and new representatives to the meeting.

2. Minutes of the last meeting and Matters Arising.

2.1 The minutes of the last meeting held on 8th May were agreed.

3. Agency update

3.1 Changes within MHRA

MHRA reported as follows:

- Dr Christian K Schneider has been announced as the new Director of The National Institute for Biological Standards and Control (NIBSC) following the retirement of outgoing Director, Dr Stephen Inglis:

https://www.gov.uk/government/news/new-nibsc-director-announced

3.2 Changes within I,E&S

MHRA reported as follows:

- The British Pharmacopoeia team have launched a new website that combines the previous two websites. See the following link for a short presentation: https://www.youtube.com/watch?v=dTUgiC5pF3I

4. Inspectorate update

4.1 Operational

4.1.1 ***Inspectorate staff changes & recruitment***

MHRA reported with regards to staff changes and recruitment within the GDP and GMP teams:

GDP

The GDP team have recently recruited 3 new inspectors. They will join the team within the next 1-2 months which will take the team up to its full complement of 18 inspectors. 3 inspectors have also been promoted to senior inspectors. The numbers of GDP applications being received are now fairly stable. The situation will be reviewed in future to determine if additional inspectors are needed.

GMP

MHRA reported that it was still actively recruiting new GMDP inspectors. There were 2 successful candidates at a recent assessment centre and a further assessment centre is planned for November to fill remaining posts. Once trainees are accredited, the team will be in a position to address current backlogs.

The inspection workload is being managed on RBI principles. The proposed inspection dates within GMP reports fit into a wider risk based inspection planning process within which the overall workload is prioritised based on risk. This process also accounts for the need to re-inspect facilities within 3 years to maintain “accepted currency” of GMP certificates. As such, whilst sites may not be re-inspected in line with the proposed dates within their reports, that is because there are facilities that are higher risk and therefore take priority. The GMP Inspectorate’s aim is to maintain the 3 year re-inspection window for all

UK based GMP sites, and in the main they have been successful in this regard.

4.2 Providing Authoritative Information

4.2.1 ***Inspectorate Blog***

MHRA presented slides on the new MHRA Inspectorate Blog. See Annex 1.

MHRA welcomed ideas from members on future blog topics.

4.2.2 ***Agency Symposia***

MHRA reported that all 4 days for the London event in December 2015 are fully booked with approx. 130 people on the waiting list.

Availability for the 1 day GDP only event in Glasgow on Tuesday 12th January is limited to 60 remaining places.

GDP agenda items include:

- What's new in the world of GDP
- Enforcement activities - Impact of the falsified medicines directive
- Export and Introduction
- Expectations of a GDP inspection including data integrity
- Complex business models - contracting across GDP
- Top deficiencies - causes and corrective actions
- Distance selling and new logo

Members queried whether the symposia could be held at another time of year as December is traditionally a busy month and also if the symposia could be made available as a webinar. MHRA confirmed that both options had been explored with internal Comms colleagues, however, neither was considered viable.

4.2.3 ***Publications***

The Orange/Green Guide

MHRA reported that it intends to produce a 2017 edition of both the Orange Guide and Green Guide. The new editions of the guides will have all the revised Commission guidance that is currently in the electronic versions on Medicines Complete.

For the Orange Guide this will include the revised GMP Annex 16 which should be on Medicines Complete shortly.
Members were invited to provide suggestions for specific topics that they may find useful that MHRA has not already provided guidance on.

4.2.4 ***Data Integrity Guidance***

MHRA reported on the work the GMP Inspectorate has carried out regarding data integrity.

From a GMP perspective, the GMP published guidance has not changed since the last meeting. Since that meeting a series of 3 articles relating to Data Integrity (DI) have been published on the inspectorate blog. These were written by David Churchward. The first one published in June looked at the impact of organisational culture upon data integrity issues. The second, published in July, explored the ALCOA acronym (attributable, legible, contemporaneous, original and accurate) and the final instalment published in August looked at the topics of performing “trial injections” within analysis runs and how the companies relying on each other within the supply chain can monitor data integrity to ensure they can rely on one another’s data.

In terms of inspections, inspectors are raising issues related to the DI guidance on site and continuing to present within a number of arenas on this topic.

The main in-house work at present on DI is working on a GxP guidance document applicable to GMP, GDP, GLP, GCP and GPvP. The inspectorate are conscious of the need for a consolidated guidance document that will apply across all GxPs as many companies, particularly on the laboratories side, work across a number of GxPs and there is an obvious need to be consistent across the board. A cross inspectorate group is working on this and it is hoped that guidance will be published within the next few months.

On an international level, the UK is the co-rapporteur for developing guidance on data integrity for EU GMP. This will probably be situated in Part 3 of EU GMP. It is being produced in conjunction with other international guidance (PIC/S and WHO) and also FDA guidance on the matter.

4.2.5 ***Deficiency Trend Data***

MHRA reported on deficiency trend data. A 2013 MHRA-industry focus group on deficiency trending made recommendations to change the presentation of data to better meet stakeholder needs. The majority of these recommendations were actioned in the trend data published in 2014.

The remaining improvements required a different approach to collection of data, enabling analysis of findings at paragraph level of the GMP guide. A tool to enable this trending has been developed, and is in the process of being populated with data from 2015 MHRA inspections of dosage form sites (UK and overseas).

Analysis of this data is anticipated by the end of the year.

Following the trial with GMP data, future progression will include inspections to Part II of the GMP guide (APIs), and GDP sites.

5. RP Training Standard

5.1 Cogent presented slides on progress in relation to the training standard for Responsible Persons (RP). See Annex 2.

MHRA clarified that whilst it would not be mandatory for RPs to have undergone RP Training, companies that had sent their RPs on an accredited course may be viewed as lower risk which would feed into the RBI process. Companies that had not had RP training may be viewed as a higher risk and would also need to demonstrate that they meet the RP gold standard by other means.

6. Support for Innovation

6.1 ABPI presented slides on the work of the Medicines Manufacturing Industry Partnership (MMIP) in relation to supporting innovation. See Annex 3.

6.2 MHRA reported on activities carried out by the agency in support of innovation. MHRA are involved in various areas including:

- Working with the Catapult Programme on innovation in the following areas: high value medicines, precision medicines, cell therapy and medicines technologies.

- Supporting various groups including the UK Regenerative Medicine Platform, the London Regenerative Medicines Network and the ATMP Manufacturing Community

- EMA's Adaptive Pathways MHRA involvement:
- early discussions that shaped communications and the pilot project
- review of submissions (>30) and 'safe harbour' discussions

- Innovation Office:
- applies to all 3 areas of MHRA, running for 2 years and now received approx. 230 enquiries,
- recent increased rate of submission – helpful effect of case studies published via MMIP or more confidence / familiarity to make submissions
- 3 more case studies in the pipeline for manufacturing and 2 for clinical trials

6.3 MHRA brought to members' attention that the agency is hosting an Innovative Medicines symposium on 30th November mainly focussed around the product licensing aspects.

7. International Interactions

MHRA reported on the Inspectorate's recent international activities:

7.1 Joint Audit Programme

MHRA were recently audited as part of the Joint Audit Programme (JAP). The auditing team were made up of 3 inspectors from other member states (France, Finland and Spain) and were accompanied by 2 observers from the USFDA (see below on Mutual Reliance Initiative). The week-long audit focused solely on GMP. The two main drivers for the process were to verify equivalence and consistency of the implementation of European legislation and the practical application of GMP standards by national inspection agencies across the EEA.

Overall the outcome was very positive. The agency was found to be compliant with 73 indicators. Five indicators were partially fulfilled and further clarification was requested for some elements of the legal framework for inspections. The audit report should be available in December. MHRA agreed to write a piece for the Inspectorate blog in the New Year once the process has been formally completed.

ACTION: MHRA

7.2 Mutual Reliance Initiative

MHRA provided an update on the Mutual Reliance Initiative:

Each year, regulatory authorities from the EU and US inspect many manufacturing sites of medicinal products on their own territories as well as around the world.

Launched in May 2014, the Mutual Reliance Initiative is a strategic collaboration between EU regulatory authorities and the US-FDA to evaluate whether we have comparable regulatory and procedural frameworks for inspections of manufacturers of human medicines so that we can rely on each other's information. Both EU regulators and FDA have dedicated teams to assess the risks and benefits of entering into a mutual reliance agreement.

For the EU, the dedicated team is composed of officials from Member States (UK, Poland, France and Croatia), the European Medicines Agency (EMA) and the European Commission (DG SANTE). This team works in close connection with the GMP/GDP Inspectors Working Group coordinated by EMA. Regular reports are also provided to the Pharmaceutical committee and Heads of Medicine Agencies (HMA).

As part of the JAP audit, 2 inspectors from the USFDA observed the process. Whilst the JAP audit focussed on the GMP systems of the MHRA, the USFDA focus was on the JAP process itself.

MHRA has already led an assessment of the USFDA accompanied by representatives from other member states.

The goal is to determine whether FDA and EU inspectorates provide comparable—but not necessarily identical— oversight with respect to Good Manufacturing Practice for the manufacturing of medicines for human use. Following this a scoping exercise will commence to determine the scope of any mutual reliance.

7.3 ICMRA

MHRA reported on the latest developments around the GMP project carried out within the International Coalition of Medicines Regulatory Agencies (ICMRA). A pilot has now been completed to determine if it is feasible to take outcomes of other regulators' inspections (international) and make a decision based on those i.e. a desktop assessment. MHRA has now proposed a phase 1 implementation of the process and this will be reviewed at the next ICMRA meeting. The proposal would be to take a small group of regulators and implement with a limited scope with the ultimate goal being to reduce duplication of inspections globally.

7.4 India

MHRA has signed a memorandum of understanding (MoU) with its counterpart body in India:

https://www.gov.uk/government/news/uk-and-india-regulators-agree-deal-for-closer-collaboration-to-improve-public-safety

MHRA are now aiming to sign more detailed MoUs with individual key states within India around information sharing.

7.5 PIC/S

There will be 48 members by January 2016. MHRA will chair PIC/S in 2016/17. Paul Hargreaves will be the chairperson representing MHRA. Mark Birse will chair the sub-committee on communication. As part of this, the agency will be hosting the annual PIC/S seminar which will be held in Manchester. The focus of the seminar will be around 'Inspectorates of the future' looking at the direction of change in industry and working more closely in future.

8. Qualified Persons

8.1 MHRA reported on the action taken since the last meeting around a possible shortage of QPs following the report published by Cogent in 2014. MHRA has held discussions with ABPI and JPB-QP on the matter. Further discussions are needed although it is likely that the MHRA will take the lead on the matter. A further update will be provided at the next GMP-GDP CC meeting although it may be the case that a paper will be circulated to the group to canvass opinion in the interim. **Action: MHRA, JPB-QP, ABPI**

8.2 Transitional QPs

Under the Clinical Trials Regulation 536/2014, Article 61(2b), QPs will need to fulfil the conditions of qualification set out in Articles 49(2) and (3) of Directive 2001/83/EC. There is no reference to the 'grandfather' provisions described in Article 50 of Directive 2001/83/EC.

There is some concern over the status of transitional QPs that were recognised under the transitional arrangements under SI 2004/1031 when the Clinical Trials Directive was implemented in 2004.
Article 49(2) of Directive 2001/83/EC provides a lot of detail about the academic level, length of study, and topics to be included. A number of the applicants who applied under the 2004 transitional arrangements had HNC/HND qualifications (typically 2 year study) supplemented by additional post graduate certificates, diplomas and IMP QP module training. The Inspectorate adopted a pragmatic approach and made use of the flexibility within 2001/83/EC to ensure that applicants provided evidence of adequate knowledge of the subjects involved in cases where the evidence of the formal qualifications do not fulfil the

criteria laid down in Article 49(2).

The agency is well aware of the potential impact to UK business and personal careers. Legal advice is currently being sought to confirm that the assessment on eligibility can still be considered valid and consider how MHRA could issue successful applicants with some form of eligibility certificate (like the permanent provision QPs receive from the Joint Professional Bodies) to show they have been assessed by MHRA as meeting the requirements of Art 49 (2) and (3) with respect to IMPs, which should help to justify their status and standing for trials across Europe. This would only apply to applicants who were assessed and acknowledged as transitional QPs under the 2004/1031 arrangements. Any new applications QPs wanting to specialise in the IMP sector would need to go through the permanent provision route.

9. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

9.1 Safety Features

The European Commission has adopted the delegated act on safety features on 2nd October. The safety features will consist of an anti-tampering device on the outer packaging and the application of a unique identifier. The unique identifier will enable wholesalers and those who supply medicines to the public, to verify the authenticity of individual packs as to their authenticity by interrogating a repository system of unique identifiers. The national repository system is to be funded by manufacturers and MAHs.

The normal consultation period of 2 months may be extended to 4 months - following the end of that period, Member states will then have 3 years to implement. MHRA are now working with the Department of Heath to develop the UK's approach to implementation, including our position on the flexibilities within the act. There are some concerns which have been raised by industry and the agency is working to develop the best approach moving forward.

The European Commission has been engaging with Member States on implementation and the first expert group meeting happened on 19th October.

9.2 Common Logo

MHRA reported on the latest developments regarding the requirement for online sellers of medicines to display a common logo on their website. MHRA has implemented a new IT system to accommodate the application process and this went live on 1st July.

This is a new regime for online sellers of medicine so the agency is being realistic with regards to enforcing the requirement to display the EU logo and working with retailers to encourage compliance. More than 300 applications have been received, many of which have been processed already. MHRA anticipates an estimated 4000 applications will be received.

The output for the new system can be viewed online and the public can report those sellers who do not display the logo.
MHRA is currently consulting on the fees for registration and has proposed to introduce an application fee of £100, and an ongoing annual service fee of £97.

Next year the Communications division will be delivering a public awareness campaign.

9.3 GDP obligations

MHRA highlighted specific GDP expectations around due diligence that has come about due to the FMD:

- WDA(H) holders should actively question suppliers if they are offered products that are not usually available or are available in unusual quantities or prices. If the WDA(H) holder suspects that a product is not legitimate, they should contact the agency.

- Wholesalers should be vigilant when supplying customers where the product ordered falls outside of the customer's usual business plan e.g. a pharmacy that does not hold a WDA(H) purchasing a large quantity of a product they would not usually purchase.

- The supplier should exercise due diligence for the condition of the product and maintenance of cold chain (if applicable) whilst in transit. This requirement extends to licenced premises that may hold the product during transit. This requirement is especially pertinent to exporters of medicines.

10. Feedback from the EMA

10.1 GMP/GDP Inspectors Working Group

MHRA reported on the work of the Inspectors Working Group:

Legislative changes:

- GMP Directive 2003/94/EC (GMP for FP and IMP)

- to be repealed and replaced by two separate acts - GMP for IMPs and GMP for finished products.
- consultations ongoing

GMP updates - published:

- Annex 16:
  - published October 2015
  - includes changes to reflect increased global manufacturing and more complex supply practices
  - intended to harmonise expectations across EU
  - coming into effect April 2016

Ongoing GMP updates:

- Annex 13:

  - updated GMP guidelines for IMPs have gone out to consultation. The document will eventually replace Annex 13.
  - MHRA are rapporteur

- Annex 1:
  - been out for consultation as early stage concept paper.
  - MHRA are rapporteur
  - joint piece of work between EC and PIC/S
  - new draft expected Q1 2016
  - associated with 2 other pieces of work which may be completed sooner than Annex 1:
    - WFI manufactured by technologies other than distillation
    - biofilms

- Annex 21: 'Importation of Medicinal products':
  - will be linked to Annex 16, providing further guidance
  - early consultation been carried out
  - no timetable as yet

- Annex 17:
  - broaden from current release of terminally sterilised products to align with QWP guideline on real time release testing (RTRT)
  - currently at consultation stage

- ATMP:
  - review following Commission report with GMP (IMP and FP) changes
  - targeted consultation ongoing

- Compliance Management process and Data Integrity:

- widen process across other member states
- MHRA are rapporteur

- Guidance for consistent interpretation by inspectors of Chapter 3 and 5 'dedicated facilities'.
  - PIC/S working group led by MHRA
  - early stages

Other work:

- *Proposal for reflection paper on GMP obligations for MAHs*
- *API white listing expanded to include Brazil and Israel*

10.2 Medicines Shortages

MHRA reported on work initiated by EMA, working with Member States and an inter-association task force to prevent shortages. A Medicines Shortages Forum was hosted by EMA on 9th October. This was the second Forum hosted by EMA on this important topic. A diverse range of stakeholders representing medicines regulators, healthcare professionals, patients and the pharma sector (with distributors) attended. FDA joined by phone.

The Forum was very open and constructive. Progress updates were given on work done after the first meeting, including ISPE and PDA. The Irish and French regulators gave interesting presentations on their approach to medicines shortages. There was discussion about what regulators could do to encourage companies to utilise the tools developed by ISPE and PDA (e.g. by inspectors). EMA stated that revisions to the introduction, chapter 1 of the GMP Guide and the Site Master File with respect to shortages were proposed. Further work by the EMA Virtual Group on Shortages was also identified e.g. a definition of a shortage and metrics.

11. Any other business

11.1 The Inspectorate are looking at how to streamline operations and make them more efficient. One area that has been identified is external stakeholder meetings where common topics may be repeated at separate meetings across GxPs. MHRA has held a Stakeholder Engagement day in the past for other GxPs in place of a joint committee meeting. The day is split in two with one part addressing common topics across the GxPs and the other addressing topics that are specific to each GxP.

MHRA welcomed comments/suggestions on carrying out something similar for GMP-GDP as well as any other comments on the content, format, duration and frequency of the GMP-GDP CC meeting. MHRA endeavoured to circulate a list of stakeholder meetings the division takes part in to aid this process.

12. Date of next meeting

April/May 2016